

# **Inclisiran and Bempedoic Acid for Patients with Heterozygous Familial Hypercholesterolemia and for Secondary Prevention of ASCVD: Effectiveness and Value**

## **Revised Background and Scope**

**August 3, 2020**

## **Background**

Atherosclerotic cardiovascular disease (ASCVD) encompasses a set of common, complex, and burdensome conditions. Three prevalent types of ASCVD are coronary artery disease, peripheral artery disease, and cerebrovascular disease, all of which result from atherosclerosis, a chronic degenerative process involving fat and cholesterol build-up in the arteries that is commonly known as “hardening of the arteries.” Over the life course, ASCVD can result in angina, claudication, myocardial infarction, or stroke, among other problems. Risk factors for ASCVD include diabetes mellitus, hypertension, obesity, smoking, and elevated levels of cholesterol, particularly low-density lipoprotein cholesterol (LDL-C).

Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disorder of cholesterol metabolism which results in very elevated plasma concentrations of LDL-C and premature ASCVD.<sup>1</sup> Heterozygous FH (HeFH) is the most common form of FH, affecting approximately 1 in 250 people in the US, with men and women equally affected.

Overall in the US, over one-half of adults are estimated to have some form of ASCVD<sup>2</sup> and ASCVD remains the leading cause of death.<sup>3</sup> The financial burden of ASCVD is also substantial, with total costs of the disease expected to reach \$1.1 trillion by 2035.<sup>2</sup> Between 2007 and 2013, death rates from ASCVD decreased for all race/ethnic groups in the United States but disparities in the overall burden of ASCVD continue to exist according to race/ethnicity and sex. The overall rates of death attributable to ASCVD in 2013 were 356.7 per 100,000 for non-Hispanic black men, 270.6 per 100,000 for non-Hispanic white men, 197.4 per 100,000 for Hispanic men, 246.6 per 100,000 for non-Hispanic black women, 183.8 per 100,000 for non-Hispanic white women, and 136.4 per 100,000 for Hispanic women.<sup>4</sup>

Treatment of patients with HeFH and those with established ASCVD includes lifestyle and behavior modification (i.e., diet, weight reduction, physical activity, smoking cessation) for all patients to slow or potentially reverse the atherosclerotic process. Risk factor management is also a staple of

care, including blood pressure control, treatment with statins and other cholesterol-lowering agents, and antiplatelet therapy with aspirin or other agents. When necessary, surgical or percutaneous revascularization is also used to treat the condition.

Even with the aforementioned treatment options, patients with HeFH and established ASCVD remain at high residual risk for further major atherosclerotic cardiovascular events, particularly if LDL-C levels remain elevated. Thus, there is an important public health need for additional treatment options to improve outcomes for patients at risk for major atherosclerotic cardiovascular events.

Two new treatments, bempedoic acid with or without ezetimibe (Nexlizet™ and Nexletol™, Esperion Therapeutics, Inc.) and inclisiran (Novartis), are proposed as the focus for this review. Bempedoic acid is an orally administered inhibitor of adenosine triphosphate citrate lyase. It received FDA approval in February 2020 as an adjuvant oral therapy for adults with HeFH on maximal statin therapy or with established ASCVD requiring additional LDL-C lowering. Inclisiran is a small interfering RNA agent targeting hepatic PCSK9 synthesis. It is delivered as a subcutaneously administered injection given twice yearly. A new drug application was submitted to the FDA in December 2019 for inclisiran for use in secondary prevention of ASCVD and patients with FH, with a regulatory decision expected in the latter half of 2020.

## **Stakeholder Input**

This scoping document was developed with input from a diverse range of stakeholders, including patient groups, clinicians, researchers, payers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with these stakeholders, additional open input submissions from the public, and comments on the draft scope. Among the changes in this updated scoping document that benefited from stakeholder input are: 1) new language clarifying the subpopulations of interest within the clinical and the economic sections of the review; 2) clarification of the basis of clinician concerns about the potential risks of unknown side effects as a result of inclisiran's dosing schedule; 3) new language highlighting disparities in cholesterol treatment as a key concern and the addition of more contextual factors that stakeholder groups felt should be considered during the review.

Patient groups highlighted that FH is underdiagnosed and that patients with FH are often undertreated despite their very high risk of CVD events beginning at a young age. Additionally, patients with FH often have events earlier in life and during years of prime productivity, so their lives may be impacted by the disease for a longer time horizon than other ASCVD patients. Accessibility, affordability, impact of therapies on health care utilization, and gaining a full understanding of impact of the new therapies on the patient experience were other concerns brought forth by patient groups.

Both clinicians and patient groups were concerned about underlying health and health care disparities in high cholesterol treatment by factors including race/ethnicity, gender, insurance status and quality of care. For example, women and racial/ethnic minorities are less likely to receive statin therapy or achieve LDL goals.<sup>5</sup> Insurance status may also play a role in uptake of therapy, as uninsured patients and those with Medicaid may be less likely to have access to newer, costlier therapies. In addition, the lack of adequate inclusion of racial/ethnic minorities in clinical trials of new therapies was identified as a barrier to being able to evaluate whether there may be differential effects of therapies in these subpopulations.

Clinicians discussed the potential role of inclisiran and bempedoic acid with or without ezetimibe in the context of treatment of HeFH and secondary prevention of ASCVD. They reported that with currently available data, inclisiran would be considered as an option having generally similar LDL-lowering ability as the PCSK9 inhibitors but without confirmatory trial data on CVD outcomes until ongoing outcomes trials are completed. Clinical experts and patient groups both highlighted inclisiran's potential benefits for patient adherence to treatment with its twice-yearly dosing compared to every two-week dosing for PCSK9 inhibitors. Some clinicians said they would be cautious about adoption of inclisiran given its relatively limited safety experience and concern that there is a risk of prolonged side effects from a drug formulated for an extended dosing interval. Bempedoic acid and the bempedoic acid/ezetimibe combination therapy were viewed as most helpful in statin-intolerant patients and those who are close to their LDL goal but do not wish to take an injectable drug. Some clinical experts highlighted concerns regarding bempedoic acid side effects such as increased uric acid levels, a negative feature in comparison to ezetimibe, which is considered to be essentially free of side effects. Clinicians also discussed the anticipated challenges with insurance coverage for both inclisiran and bempedoic acid, expressing frustration with the prior authorization process experience with PCSK9s, which has delayed access to therapy for many patients.

Manufacturers highlighted that consideration should be given to the impact of potential differences between treatments beyond LDL-C lowering, including mode of delivery, drug administration considerations (e.g., in a physician's office or self-administered), dosing interval, adherence, and effects on other disease parameters (e.g., hemoglobin A1c, high-sensitivity CRP).

ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

## **Report Aim**

This project will evaluate the health and economic outcomes of inclisiran and bempedoic acid with and without ezetimibe as additive therapies to existing medical management in patients with HeFH and for secondary prevention in patients with established ASCVD. The ICER value framework

includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as the potential benefits from new mechanisms of action, treatments for historically underserved populations, and reduced burdens for caregivers – are considered in the judgments about the clinical and economic value of the interventions.

## Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events (AEs). ICER welcomes data from patient registries, studies using patient-reported outcomes, and high-quality sources of real-world evidence. Our evidence review will also include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's [grey literature policy](#)).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

## Populations

The population of interest for this review is adults with elevated LDL-C levels despite treatment with maximally tolerated lipid lowering therapy. We will consider evidence across relevant populations including all patients with HeFH (primary and secondary prevention) and patients with established ASCVD (secondary prevention). As noted below in the description of the scope for the Comparative Value Analysis, not all patient subpopulations will be evaluated in the economic model.

We will evaluate the evidence, where available, on the following subpopulations:

- Patients with HeFH with and without established ASCVD (primary and secondary prevention)
- Patients with established ASCVD at relatively higher risk (e.g., patients with a recent MI)
- Patients with statin intolerance

## Interventions

The interventions of interest for this review will be inclisiran (Novartis) and bempedoic acid with or without ezetimibe (Nexlizet™ and Nexleto™, Esperion Therapeutics, Inc.) added to maximally tolerated lipid-lowering therapies.

## Comparators

We will compare the use of each of the interventions in conjunction with maximally tolerated background lipid-lowering therapy versus ongoing maximally tolerated lipid-lowering therapy (i.e., intervention vs. placebo arms of clinical trials). We will explore comparing the interventions to each other and to PCSK9 inhibitors via network meta-analysis.

## Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
  - All-cause mortality
  - CV mortality
  - Myocardial infarction
  - Stroke
  - Unstable angina
  - Revascularization
  - Health-related quality of life
- Other Outcomes
  - LDL-C
  - High-density lipoprotein cholesterol (HDL-C)
  - Total cholesterol
  - Non-HDL-C
  - Triglycerides
  - Apolipoprotein B
  - Lipoprotein(a)
  - High-sensitivity C-reactive protein (hsCRP)
  - PCSK9 level (for inclisiran and PCSK9 inhibitors)

- Safety
  - Treatment-emergent AEs, including:
    - Muscle-related AEs
    - Increase in liver function tests
    - Tendon rupture
    - Uric acid level
    - Injection-site reactions
    - Discontinuation due to AEs
    - Serious AEs, including:
      - Death

## **Timing**

We will consider evidence from studies with at least four weeks of follow-up.

## **Settings**

We will consider all relevant settings.

## Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

**Table 1.1. Potential Other Benefits or Disadvantages and Contextual Considerations**

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

## Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of the bempedoic acid/ezetimibe combination therapy and inclisiran, each relative to their own control arm (of maximally tolerated lipid-lowering therapy including statin and ezetimibe), in patients with established ASCVD. Note that the clinical review will include a broader target population, including patients with HeFH who do not have ASCVD, whereas the quantitative section of the comparative value analysis will focus on individuals with established ASCVD. Similarly, the clinical review will also examine bempedoic acid alone as well as in combination with ezetimibe, whereas the comparative value analysis will only examine the combination pill.

The model structure will be based in part on a literature review of prior published models of cardiovascular disease. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis from a modified societal perspective. The target population will consist of patients with established ASCVD who need additional lipid-lowering despite maximally tolerated statin therapy. The clinical review will evaluate evidence on differential effectiveness of treatments across patient subgroups and if there are important differences identified the model will explore relevant subgroups of patients, potentially including:

- Patients with HeFH and established ASCVD
- Patients with an acute MI in the past year (one important “high-risk” subpopulation of ASCVD patients)
- Patients with statin intolerance

Our base-case analysis will incorporate a lifetime analytic horizon. Future costs and benefits will be discounted at 3% per year.<sup>6</sup>

The model will consist of health states including prior history of MI, prior history of stroke, prior history of both MI and stroke, death from cardiovascular causes, and death from non-cardiovascular causes. A cohort of patients will transition between states during predetermined cycles (of three months) over a lifetime horizon, modeling patients from treatment initiation until death. Each cycle will carry a risk of recurrent events including acute coronary syndrome and ischemic stroke, along with death from cardiovascular and other causes. Key model inputs will include transition probabilities, quality-of-life values, and health care costs.

Treatment effectiveness and rate of AEs will be derived from the evidence review described above. Health outcomes and costs will be dependent on time spent in each health state and the incidence of clinical events (including cardiovascular events and AEs related to the therapies). The health outcome of each intervention will be evaluated in terms of major adverse cardiovascular events averted, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years

gained ([evLYG](#)). Quality-of-life weights will be applied to each health state, including decrements for serious AEs. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious AEs. In addition, productivity changes and other indirect costs will be included in a separate analysis as available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per major adverse cardiovascular event averted. In sensitivity analyses, we will examine the robustness of our findings to uncertainty in key input parameters.

In addition, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found [here](#).

## **Identification of Low-Value Services**

As described in its Value Assessment Framework for 2020-2023, ICER will include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's [Value Assessment Framework](#)). These services are ones that would not be directly affected by inclisiran and bempedoic acid with or without ezetimibe (e.g., hospitalizations for cardiovascular events), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of the secondary prevention of ASCVD and HeFH beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

## References

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